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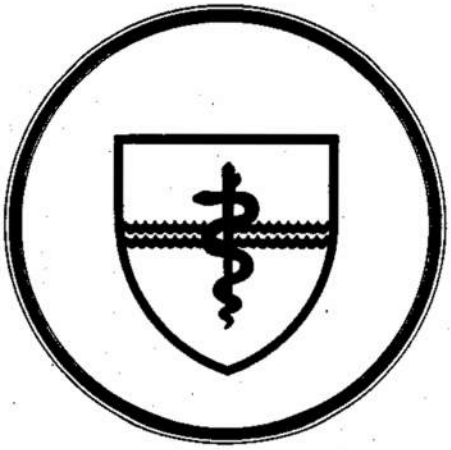

REPORT NUMBER 829

BIOCHEMICAL COMPARISONS OF TWO-HOUR EXPOSURES TO HYDROGEN-OXYGEN, HELIUM-OXYGEN AND NITROGEN-OXYGEN ATMOSPHERES AT 200 FSWG

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Naval Medical Research and Development Command
Research Work Unit M4306.02-5003 BA9K,
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23 September 1982

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SUMMARY PAGE

PROBLEM

To compare the biological safety of hydrogen-oxygen, helium-oxygen, and nitrogen-oxygen diving mixtures for use by human subjects compressed to pressures equivalent to 200 feet of sea water.

FINDINGS

When compressed for 120 minutes to simulated 200 feet of water pressure, biochemical and hematologic signs of stress were no more pronounced in divers breathing hydrogen-oxygen than helium-oxygen or nitrogen-oxygen mixtures. From several points of view, the hydrogen dives were less stresssful than those performed in the other two gaseous atmospheres. For example, general distress and nausea were experienced during the nitrogen dives and signs of metabolic stress occurred during the recovery from the helium dives. Biochemical data lend support to the medical observation of biological safety of hydrogen-oxygen diving mixtures under the conditions tested.

APPLICATION

The future supply of hydrogen, which may be produced from water, is essentially unlimited compared to a limited supply of helium. Hydrogen is also lighter than helium and will provide less dense breathing mixtures if it proves biologically acceptable as a component of diving atmospheres. Pioneering experiments indicate the feasibility of the use of hydrogen-containing atmospheres down to the pressures that have been tested and indicate that further investigations are in order.

ADMINISTRATIVE INFORMATION

This research was conducted as part of the Naval Medical Research and Development Command Work Units M4306.02-5003 BA9K, MF51.524.014-9016 and MF58527.02B-0001. It was submitted for review on 10 Feb 1982, approved for publication on 23 September and designated as NSMRL Rpt. No. 829.

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ABSTRACT

Biochemical and hematologic analyses were performed on urine and blood samples collected from three civilian divers following exposure for 120 minutes to hydrogen-oxygen, helium-oxygen and nitrogen-oxygen breathing mixtures at simulated pressures of 200 feet of sea water (FSWG). Normoxic environments were maintained except when symptoms of hypoxia, which developed in the subjects breathing nitrogen-containing mixtures, were relieved by additional oxygen. Biological sampling was possible from selected dives during a series of two dives by each subject in each of the gaseous mixtures.

An overall evaluation of the biochemical and hematologic signs of stress point to no greater or somewhat reduced stress in divers breathing hydrogen-oxygen compared to helium-oxygen mixtures. Greatest differences were noted during the earlier phases of recovery from the dives. Measurable biological changes as a result of nitrogen-oxygen diving were confounded by outward signs of distress such as nausea and increased frequency of decompression sickness. Biochemical data lend support to the general medical observation of biological safety of hydrogen-oxygen mixtures under the conditions tested. The potential advantage of decreased density and greater availability of hydrogen compared to helium indicate that further testing of hydrogen-containing atmospheres is warranted.

INTRODUCTION

The use of any breathing mixture currently available for diving operations presents biological hazards with which divers and diving supervisors must contend. Compressed air, for example, breathed at depths greater than 150 FSWG produces recognized and predictable narcotic effects (6,10, 25), while symptoms related to oxygen toxicity occur in compressed air at lesser pressures especially if lengthy exposure times are employed (3,5,27). Decompression sickness probably caused by bubble formation in tissues, is a particularly infamous problem and is undoubtedly the most common complication relating to work at pressures greater than one atmosphere (4).

Helium oxygen diving environments, which have allowed many successful dives to depths greatly in excess of those possible with other gas mixtures, may lead to the high pressure nervous syndrome (HPNS), or "helium tremors", if appropriate precautions are not exercised (8,9,12). Other inert gases -- argon, krypton, xenon, and neon -- have been studied as possible diluting agents for oxygen in breathing mixtures but are limited in availability and, at sufficient depth, have generally proven to possess many of the narcotic properties of nitrogen (7,30).

Hydrogen, the lightest gas, has received limited consideration as a major component of breathing media for divers and is the subject of the work to be described here. While hydrogen has been reported to produce greater narcotic effects than helium (12,14), its wider availability and potential cost advantage make it a worthy candidate for investigation as a carrier or dilutent of oxygen for use under pressure. Furthermore, the narcotic properties of hydrogen are counterbalanced by the low tendency of this gas to produce the "high pressure nervous syndrome", HPNS (12). The most obvious safety problem arising from the use of hydrogen, that of its explosive nature in the presence of oxygen, has been considered by several investigators and reviewed by Edel (18).

The present series of investigations was undertaken to broaden the available information concerning the biological safety of hydrogen-oxygen dives for human subjects. In this work, comparable series of dives were made to simulated depths of 200 feet of sea water (FSWG) for 120 minutes in nitrogen-oxygen (N_2-O_2 or nitrox), helium-oxygen (He-O_2 or heliox), and in hydrogen-oxygen (H_2-O_2 or hydrox) mixtures.

MATERIALS AND METHODS

The entire series of dives, performed at the facilities of Michel Lecler, Inc., Harvey, LA, has been described by Edel (19). Because of logistic limitations, biochemical data could not be obtained from all of the eight dives made by four civilian divers using the three gas mixtures: 97% N_2-3% O_2, 97% He-3% O_2 and 97% H_2-3% O_2. The number of biological samples available for analysis from each of the series of dives is shown in the accompanying figures. The dives were performed by one subject per day with the gas mixtures used in the order: He-O_2, H_2-O_2, N_2-O_2. All He-O_2 dives were completed before the H_2-O_2 series began and similarly these were finished before the N_2-O_2 dives. Four days or more intervened between dives by any individual subject.

Blood and urine sample collections from the subjects were conducted by a member of the Naval Submarine Medical Research Laboratory staff who also performed blood cell counts, hemoglobin, hematocrit, plasma fibrinogen, and urine protein measurements. Cell counts were obtained by standard microscopic procedures as the samples were collected. Serum and urine aliquots were frozen and returned to our laboratory for detailed chemical analyses. Methods for processing blood and urine samples have been discussed in previous reports (25,26,27,39).

RESULTS AND DISCUSSION

Data from the control and experimental periods for the various dive series are shown in Figures 1 and 2. The small number of samples collected during the very limited sampling times has necessitated the grouping of some of the data into rather broad categories. Samples were not available for cases where data are missing. The values plotted are means of all data obtained from the dives. Paired analyses of the data were performed by evaluating the median value for each subject's control period against each datum for that subject during the experimental periods. Paired comparisons of the urine data were made with the amount of each metabolic product expressed per gram of creatinine to reduce potential inaccuracies caused by the possibility of incomplete sample collection. While it is common practice to report urinary excretion data per gram of creatinine, we and others have found that this is far from an ideal method for evaluating such information (16, 39).

The use of creatinine as a reference material was especially important in this work for evaluating data collected during and after the N_2-O_2 dives in which urine volume was extremely low. The metabolite/creatinine values for the urinary components, after the N_2-O_2 dives (Figure 1) tend to make us feel that there were indeed low volumes of urine produced in connection with these dives rather than very poor cooperation on the part of the subjects in collecting urine samples. It should be noted that despite the low metabolite excretion in these cases, the creatinine-based excretion ratios were significantly higher than during the control days. Although the differences between other experimental and control data from the N_2-O_2 experiments are sizeable, they are generally not statistically different because of the few experimental samples available for analysis. The low urinary volumes following the N_2-O_2 dives raise the possibility that hormonal activity, may have influenced the excretory patterns observed.

In his overall evaluation of the dives discussed here, Edel reported not only that a higher incidence of bends occurred as a result of exposures to the N_2-O_2 regimen than with any other breathing medium, but also that two divers suffered from severe nausea and vomiting while breathing the N_2-O_2 mixture at pressure (19). The divers were also observably narcotized while using the nitrox mixtures and reported this medium to be the least acceptable among the combinations employed. Since the nausea experienced as a consequence of the 97% nitrogen environment at 7.06 ATA was relieved by changing to mixtures containing increased O_2 levels (10), it was concluded that the symptoms being observed were the result of the so-called "Chouteau effect" (13-14).

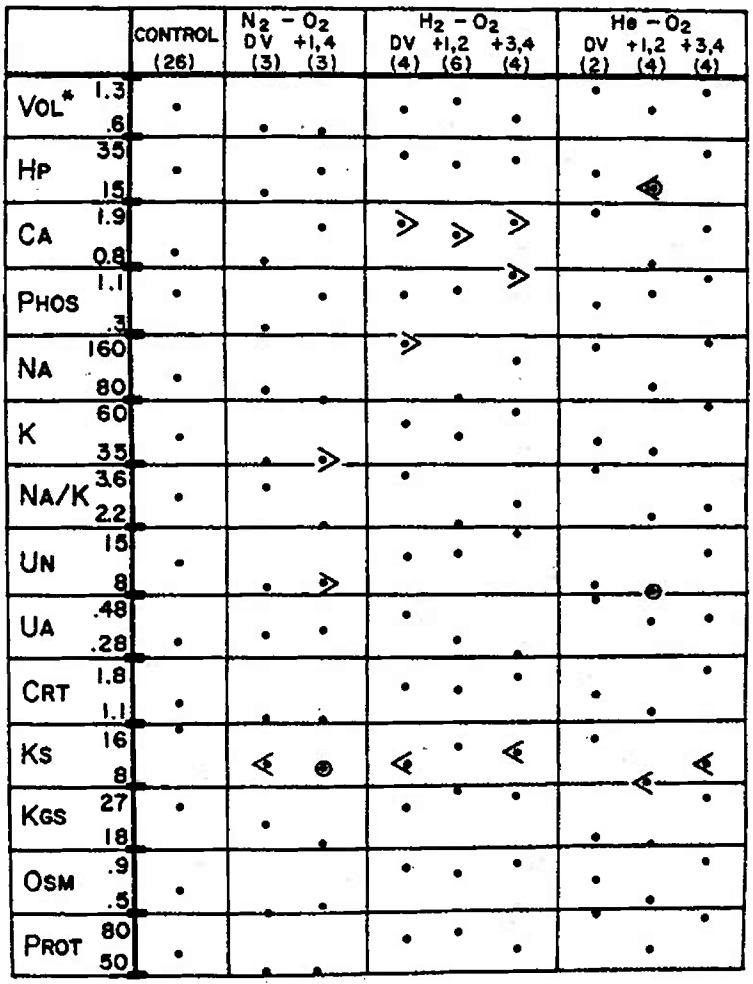

Figure 1. Urinary response to diving regimens (condensed plot for each component). *: VOL = volume, l; HP = hydroxyproline, mg; CA = calcium, g; PHOS = inorganic phosphorus, g; NA = sodium, meq; K = potassium, meq; NA/K = sodium/potassium ratio; UN = urea nitrogen, g; UA = uric acid, g; CRT = creatinine, g; KS = ketosteroids, mg; KGS = ketogenic steroids, mg; OSM = osmoles; PROT = protein, mg. All per 24 hrs. Symbols: circle = significantly different from controls at $p < .05$ by paired anslysis; < or > = significantly less than or greater than controls per g CRT by paired analysis, $p < .05$.

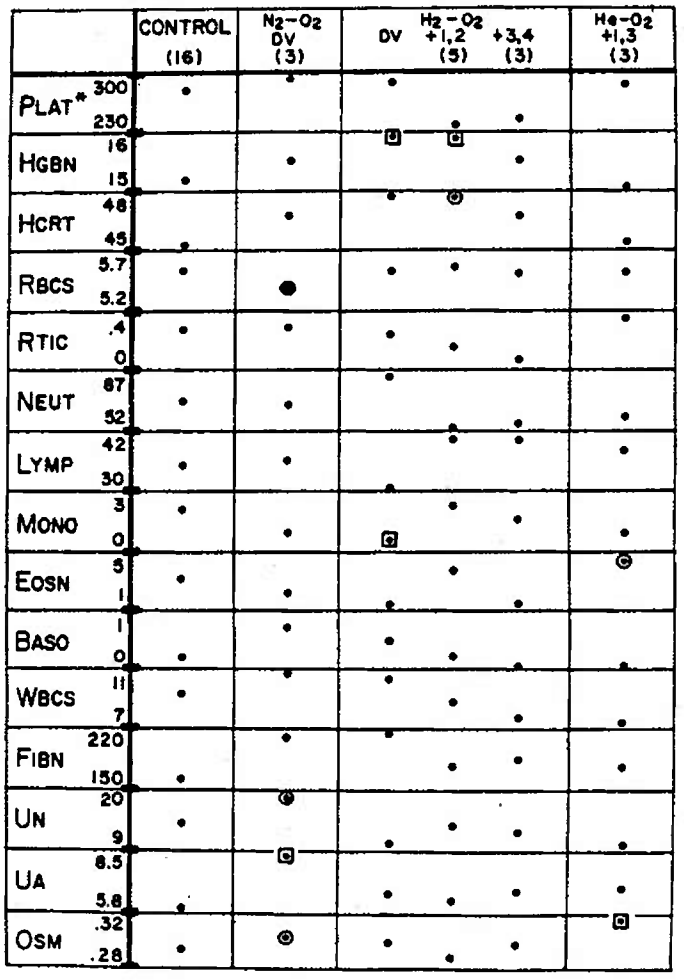

Figure 2. Responses to dives reflected by hematology and serum chemistry. *: PLAT = platelets, $10^3/mm^3$; HGBN = hemoglobin, g/dl; HCRT = hematocrit, %; RBCS = red blood cells, $10^6/mmm^3$; RTIC = reticulocytes, % RBCS; WBCS = white blood cells, $10^3/mm^3$; NEUT = neutrophils, % WBCS; LYMP = lymphocytes, % WBCS; MONO = monocytes, % WBCS; EOSN = eosinophils, % WBCS; BASO = basophils, % WBCS; FIBN = fibrinogen, mg/dl; UN = urea nitrogen, mg/dl; UA = uric acid, mg/dl; OSM = osmoles/1. Symbols: circles or squares - significantly different from controls at $p < .05$ for paired or group analysis. Results of more than one method of data handling are reported because of the small numbers of experimental values for analysis in each category. While such an approach may overstate significant differences within these data, it is useful for pointing out potential differences.

With the limited amount of data available, it is not possible to adequately determine whether the decreased concentrations of erythrocytes reported for the N_2-O_2 dives, Figure 2, are directly related to the effects of the breathing mixture. It seems unlikely that a significant number of red blood cells would have been destroyed by the increased oxygen levels during two-hour exposure periods. Visual observations made of the sera of the subjects indicated no significant hemolysis occurred in any of the samples. The hemoglobin and hematocrit data, show no indication of decreased effective oxygen carrying capacity. Evidence of some stress, however, during the N_2-O_2 dives is given by serum urea nitrogen, uric acid, and osmolality data. The higher values for these components may be related either to the decreased urinary volume excreted or to increased catabolic activity during the diving episodes or to both. Additional studies, in which fluid intake is more carefully controlled, will be required to ascertain whether the possible fluid balance disruptions suggested here may be the result of peculiar habits of the divers participating in these studies or are ascribable to the pressure schedules, work routines and/or gas mixtures used.

While the conditions in the present series of dives were quite different from those reported previously from our laboratory, earlier findings regarding urine volume output and its effects on total excretion of metabolites during and after air dives may contain clues for interpretation of the results of the nitrox dives. A strong tendency has been reported for both human divers and laboratory animals to reduce fluid intake immediately following short-term simulated dives using air (23,24), with the resulting decrease in urine volume exerting a marked influence on the total output of metabolic products. On the other hand, if conscious efforts on the part of the divers are made to maintain normal fluid intake during the periods before, during and after dives, the apparent fluid retention, ie., production of abnormally low urine volumes with consequent excretion of reduced amounts of metabolic products, is obviated (22,25).

During and immediately after the H_2-O_2dives, the increases in hemoglobin and hematocrit values, shown in figure 2, seem to indicate a hemoconcentration which began to diminish within 3-4 days after the dives. Hemoconcentration from pressure exposures is a well-recognized phenomenon (11,28,29, 34).

The urinary increases of sodium, calcium, and phosphorus relative to creatinine output during and after the hydrox dives indicate changes in electrolyte and mineral turnover resulting from the diving regimen and bear scrutiny during any additional studies involving hydrogen-oxygen breathing media. The relative changes in ketosteroid excretion resulting from the hydrox dives are similar to those following the nitrogen oxygen dives but seem less severe than those after He-O_2 exposures.

Of interest in consideration of the results of the N_2-O_2 dives are the lowered levels of ketosteroids excreted. It has been our experience in experimental dives performed under a variety of conditions that reduced ketosteroid excretion tends to be a frequent

occurrence in subjects exposed to diving and decompression stresses (22,25). In general, it appears appropriate to attribute reduced ketosteroid excretion noted during the recovery from diving operations to reduced androgenic hormone production during the stress periods rather than to a diminishment of activity of the adrenal cortex. While the concept of decreased androgen production during emotional stress has been considered under several circumstances (20,31,36), the effect of environmental and physical stresses are less clear. Since androgenic hormones are generally anabolic, it is plausible that the process of tissue repair might utilize or bind these hormonal substances. Some tissue damage from hyperbaric exposures now seems to be a rather well-established fact (1,34). Either increased androgen utilization or decreased production or both may therefore have influenced the ketosteroid values observed here.

The measurable responses to the $He-O_2$ dive series were comparable to, and for many of the biochemical data, generally indistinguishable from those of the H_2-O_2 experiments. Low urine urea nitrogen and hydroxyproline values resulted from these dives but specific interpretations of the findings can not yet be assigned. The urine ketosteroid data indicate a considerable depression in the excretion of these hormones during the four days of recovery from the dives. In accordance with the proposal of increased utilization of ketosteroids, active recovery from stress would seem to have been occurring at this time. The increased serum osmolality found during the recovery phase from the $He-O_2$ dives may reflect the lowered output of urea nitrogen and possibly sodium in the urine. No evidence of hemoconcentrations is apparent from the hemoglobin and hematocrit values.

For comparative purposes, the sums of "T" values, calculated by student's T distribution (38), for all of the biological measurements made on a particular fluid or tissue have been determined in previous experiments in an attempt to obtain an assessment of the extent of the stress being experienced during a particular period (21). It may be expected that any change reflecting increasing differences from control values indicate detrimental effects in health status under the radically altered environmental conditions studied. Subsequent work investigating mean "T" values to replace the sum of these values to compensate for varying numbers of determinations performed led to the use of probability (p) values for further improvement in stress estimation. Table 1 contains mean probability data from paired analyses comparing the results from each dive segment against the control data for each of the individual divers. The use of probability data represents some refinement in the calculation of stress experienced since a given absolute value of p has the same level of significance irrespective of sample size, whereas the T values for a given significance decrease as sample size increases. In spite of its recognized limitations, this estimation of stress has been used here in an attempt to provide means for interpreting a large collection of data generally falling within normal ranges.

The probability index, particularly for urine, indicates lower mean p values, and therefore probable increased stress levels, following the nitrox dive series when compared to the various phases

TABLE 1. Stress approximations from probability data for experimental dives and post-dive periods. Data shown are mean probability values and standard errors for comparisons of experimental to control values by paired analysis for 14 urine and 15 blood components shown in Figures 1 and 2.

Experimental	Mean p + SE
Urine:	
N2-02 Dive	.440 ± .052
N2-02 + 1,4	.306 ± .073
H2-02 Dive	.536 ± .073
H2-02 + 1,2	.476 ± .068
H2-02 + 3,4	.557 ± .054
He-02 Dive	.388 ± .056
He-02 + 1,2	.191 ± .030
He-02 + 3,4	.462 ± .071
Blood:	
N2-02 Dive	.385 ± .085
H2-02 Dive	.434 ± .062
H2-02 +1,2	.437 ± .045
H2-02 +3,4	.399 ± .062
He-02 +1,3	.463 ± .078

of the hydrox series. From our previous experience (24,25,39) and from analogy with the He-O2 dives, it would be expected that much of the stress during the recovery from the N_2-O_2 dives occurred during the first two post-dive days. Indeed, the data demonstrate that the subjects experienced greater shifts away from controls values, greater stress during and after the He-O_2 than in the H_2-O_2 series. From the very limited numbers of samples, particulary following the nitrox dives, we hesitate to estimate the relative extent of stress resulting from the He-O_2 compared to the N_2-O_2 dives. Strong indications of stress are apparent, however, during the first two days after helium-oxygen exposures.

While no currently available procedure provides an absolute evaluation of stress (32), the method employed in Table 1 supports the subjective observation concerning the stressfullness of the three diving regimens (19). Even when additional oxygen was added during the N2-02 dives, the data indicate that the dives supported by hydrogen-oxygen were probably less stressful than those employing nitrox. Similarly less stress appears to have resulted from the hydrox than from the heliox dives. The greatest advantages of using the hydrox breathing mixture seem to occur in the early phase of the recovery from the dives and would appear to be related to the relative ease with which hydrogen is removed from the tissues.

It is emphasized that with very low individual probabilities of significant changes from normality among the variables measured, the probability indices shown in the table represent only the first approximations of the extent of metabolic stress experienced in each case. A depth of 200 FSWG must also be recognized as very shallow for the use of either helium or hydrogen breathing mixtures. More extended times and greater depths must be studied before an ultimate evaluation of the medical safety and efficacy of hydrogen for diving application can be made.

Recent work of D'Aoust, et al (17) has indicated the safety of employing hydrogen for isobaric gas switching after saturation of live goats at 8 bar (231 FSW) for 17 hrs in nitrogen containing 0.3 bar oxygen. Switches from hydrogen to helium and from argon to hydrogen were performed with a moderate level of vascular gas bubbles detectable in the former instance. These studies demonstrate apparent advantages to the use of hydrogen in the sequential replacement of compressed environmental gases for operational diving protocols.

In view of the current awareness of the limitations of traditional sources of energy, considerable research is being directed toward the employment of hydrogen as an intermediate for energy storage and transport (15). As a result of this interest, it has been estimated that the world's annual production of hydrogen will increase to as much as 140 million tons by the end of this century (2). On the other hand, predictions based on current information concerning available helium resources indicate the exhaustion of the U.S. helium supplies by the year 2000 (33). Helium inevitably will become increasingly scarce and more costly as a major component of breathing mixtures. The supply of hydrogen produced primarily from the decomposition of water, however, needs only be limited by utilization requirements or development of

efficient production technology which may employ solar, nuclear, or other energy sources (2). For these reasons and for the theoretical density advantage of breathing hydrogen in compressed mixtures, careful exploration into the use of hydrogen in diving operations carries great potential significance.

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19. KEY WORDS *(Continue on reverse side if necessary and identify by block number)*
helium-oxygen diving environments; hydrogen-oxygen breathing mixtures; nitrogen-containing mixtures; ketosteroid excretion;

20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)* Biochemical and hematologic analyses were performed on urine and blood samples collected from three civilian divers following exposure for 120 minutes to hydrogen-oxygen, helium-oxygen and nitrogen-oxygen breathing mixtures at simulated pressures of 200 feet of sea water (FSWG). Normoxic environments were maintained except when symptoms of hypoxia, which developed in the subjects breathing nitrogen-containing mixtures, were relieved by additional oxygen. Biological sampling was possible from selected dives during a series of two dives by each subject in each of the gaseous mixtures. (cont'd)

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item 20--continued

An overall evaluation of the biochemical and hematologic signs of stress point to no greater or somewhat reduced stress in divers breathing hydrogen-oxygen compared to helium-oxygen mixtures. Greatest differences were noted during the earlier phases of recovery from the dives. Measurable biological changes as a result of nitrogen-oxygen diving were confounded by outward signs of distress such as nausea and increased frequency of decompression sickness. Biochemical data lend support to the general medical observation of biological safety of hydrogen-oxygen mixtures under the conditions tested. The potential advantage of decreased density and greater availability of hydrogen compared to helium indicate that further testing of hydrogen-containing atmospheres is warranted.